NITROLIPIDS AND TOCOPHEROL-NITRIC OXIDE DONORS: EFFECTS ON INFLAMMATION AND ATHEROSCLEROSIS

Homero Rubbo

Departamento de Bioquímica and Center for Free Radical and Biomedical Research, Facultad de Medicina-Uruguay

Nitrated fatty acids (nitroalkenes), including nitrolinoleate and nitrooleate, have been recently quantified in red blood cells and human plasma. Herein, we synthesized and determined the isomer distribution of nitroarachidonate ($AANO_2$) and demonstrated its ability to redirect arachidonic acid-dependent cell signaling pathways. $AANO_2$ caused cGMP-dependent vasorelaxation and modulated macrophage activation through inhibition of inducible nitric oxide synthase (NOS2) expression. This anti-inflammatory activity was related with activation of the Nrf2/ARE pathway. Cellular generation of free and esterified lipid nitroalkenes was also investigated: increased levels of cholesteryl-nitrolinoleate ($CLNO_2$) in macrophages activated by pro-inflammatory stimuli were found, concurrent with increased NOS2 expression. Moreover, $CLNO_2$ added to activated cells inhibited inflammatory responses, including pro-inflammatory cytokines expression (IL-1β, TNF). Finally, we synthesized a new class of nitric oxide donors (nitrooxy or furoxan- α-tocopherol analogs, ENOs). These compounds exhibited vasorelaxing properties and protected human low-density lipoprotein (LDL) from oxidative stress, suggesting their potential use for prevention of atherosclerosis. Moreover, our preliminary data demonstrate a significant decrease in aortic lesion formation in a cholesterol-fed LDL receptor negative mice model of atherosclerosis by ENOs treatment. All together these data reveal that nitrated lipids are formed in response to pro-inflammatory stimuli, serving as novel adaptative mediators to down-regulate inflammatory responses.

Key words: nitrated lipids, Tocopherol-nitric oxide donors, inflammation.